DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

ROCHE DIAGNOSTICS
SARAH BAUMANN
PROGRAM MANAGER, REGULATORY AFFAIRS
9155 HAGUE RD.
INDIANAPOLIS, IN 46250

October 24, 2014

Re: K142133
Trade/Device Name: Elecsys CMV IgM Immunoassay; Elecsys PreciControl CMV IgM
Regulation Number: 21 CFR 866.3175
Regulation Name: Cytomegalovirus serological reagents
Regulatory Class: II
Product Code: LFZ, JJX
Dated: August 1, 2014
Received: August 4, 2014

Dear Ms. Baumann:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Stephen J. Lovell -S for

Sally A. Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K142133

Device Name
(1) Elecsys CMV IgM Immunoassay
(2) Elecsys PreciControl CMV IgM

Indications for Use *(Describe)*
(1) Immunoassay for the in vitro qualitative detection of IgM antibodies to CMV in human serum, lithium-heparin plasma, K2-EDTA plasma, and K3-EDTA plasma. The test is intended as an aid in the diagnosis of recent or current CMV infection in individuals for which a CMV IgM test was ordered, including pregnant women.
Performance characteristics have not been evaluated in immunocompromised or immunosuppressed individuals. This test is not intended for use in neonatal screening or for use at point of care facilities. This assay is not intended for use in screening blood and plasma donors.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys immunoassay analyzers.

(2) PreciControl CMV IgM is used for quality control of the Elecsys CMV IgM immunoassay on the Elecsys and cobas e immunoassay analyzers.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

1 Section III—510(k) Summary

1.1 Introduction

According to the requirements of 21 CFR 807.92, the following information provides sufficient detail to understand the basis for a determination of substantial equivalence.

1.2 Submitter Name, Address, Contact Information

Roche Diagnostics Corporation
9115 Hague Road
Indianapolis, IN 46250

Contact Person: Sarah Baumann, MS, RAC
Phone: 317-521-3952
Fax: 317-521-2324
Email: sarah.baumann@roche.com

Secondary Contact Person: Dr. Michael Leuther, Ph.D.
Phone: 317-521-3930
Fax: 317-521-2324
Email: michael.leuther@roche.com

Date Prepared: October 23, 2014

1.3 Device Name

Proprietary Name:	(1) Elecsys CMV IgM Immunoassay (2) Elecsys PreciControl CMV IgM
Common Name:	(1) CMV IgM assay (2) PreciControl CMV IgM
Classification Name:	(1) Enzyme Linked Immunoabsorbent Assay, Cytomegalovirus (2) Single (Specified) Analyte Controls (Assayed and Unassayed)
Product Code:	(1) LFZ (2) JJX
Predicate Device:	(1) Diamedix Is-CMV IgM Capture Test Kit (K001767) (2) Elecsys PreciControl Rubella IgM (K092322)

Panel	Product Code	Classification Name	Regulation Citation	Device Class
Microbiology	LFZ	Enzyme Linked Immunoabsorbent Assay, Cytomegalovirus	21 CFR 866.3175	II
Clinical Chemistry	JJX	Single (Specified) Analyte Controls (Assayed and Unassayed)	21 CFR 862.1660	I

1.4 Device Description

(1) Elecsys CMV IgM:

Elecsys CMV IgM is a µ-capture immunoassay with streptavidin microparticles, biotinylated recombinant CMV-specific antigen labeled with a ruthenium complex and electrochemiluminescence detection. The results are determined using a calibration curve which is instrument-specifically generated by a 2-point calibration and a master curve provided via the reagent bar code. The test system contains the human serum-based calibrators intended for use with the system.

The CMV IgM assay begins with an automatic 1:20 predilution of sample with Elecsys Diluent Universal and the addition of biotinylated monoclonal anti-h-IgM-specific antibodies.

During the second incubation, CMV-specific recombinant antigen labeled with a ruthenium complex[a] and streptavidin-coated microparticles are added. Anti-CMV IgM antibodies present in the sample react with the ruthenium-labeled CMV-specific recombinant antigen. The complex becomes bound to the solid phase via interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell. Application of a voltage to the electrode induces chemiluminescent emission which is measured by a photomultiplier.

The analyzer automatically calculates the cutoff based on the measurement of Cal1 and Cal2. The result of the samples is given either as reactive or non-reactive as well as in the form of a cutoff index (signal samples/cutoff). Samples with a cutoff index (COI) < 0.7 are non-reactive. Samples with a cutoff index between 0.7 and < 1.0 are considered indeterminate (border). Samples with a cutoff index ≥ 1.0 are considered reactive.

(2) Elecsys PreciControl CMV IgM:

Elecsys PreciControl CMV IgM contains liquid control serum based on human serum. The controls are used for monitoring the accuracy of the Elecsys CMV IgM immunoassay.

The reagents and calibrators are packaged together in the Elecsys CMV IgM assay kit, while the associated Elecsys PreciControl CMV IgM is packaged separately.

The following reagents are provided in the Elecsys CMV IgM assay kit:

1. The reagent rackpack consists of reagents M, R1, and R2 and is labeled as CMVIGM:
   -M: Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.

   -R1: Anti-h-IgM-Ab~biotin (gray cap), 1 bottle, 9 mL: Biotinylated monoclonal anti-h-IgM antibody (mouse) > 500 µg/L, MES buffer 50 mmol/L, pH 6.5; preservative.

   -R2: CMV-Ag~Ru(bpy) (black cap), 1 bottle, 9 mL: CMV-specific antigen (recombinant, E. coli) labeled with ruthenium complex > 50 µg/L; MES buffer 50 mmol/L, pH 5.5; preservative.

2. CMVIGM Cal1: Negative calibrator 1 (white cap), 2 bottles of 1.0 mL each: Human serum, non-reactive for anti-CMV IgM; preservative.

3. CMVIGM Cal2: Positive calibrator 2 (black cap), 2 bottles of 1.0 mL each: Human serum reactive for anti-CMV IgM; buffer; bovine albumin; preservative.

The following are the materials that are required but not provided:

1. PreciControl CMV IgM, 8 x 1.0 mL each of PreciControl CMV IgM 1 and 2
2. Diluent Universal, 2 x 36 mL sample diluent
3. CalSet Vials, 2 x 56 empty snap-cap bottles
4. General laboratory equipment
5. Elecsys 2010 analyzer
6. Accessories for Elecsys 2010 analyzer

1.5 Intended Use

(1) Elecsys CMV IgM:

Immunoassay for the in vitro qualitative detection of IgM antibodies to CMV in human serum, lithium-heparin plasma, K_2-EDTA plasma, and K_3-EDTA plasma. The test is intended as an aid in the diagnosis of recent or current CMV infection in indiviuals for which a CMV IgM test was ordered, including pregnant women.
Performance characteristics have not been evaluated in immunocompromised or immunosuppressed individuals. This test is not intended for use in neonatal screening or for use at point of care facilities. This assay is not intended for use in screening blood and plasma donors.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys immunoassay analyzers.

(2) Elecsys PreciControl CMV IgM:

PreciControl CMV IgM is used for quality control of the Elecsys CMV IgM immunoassay on the Elecsys and **cobas e** immunoassay analyzers.

1.6 Indication for Use

Refer to Section 1.5 (Intended Use) above.

1.7 Substantial Equivalence Information

1.7.1 Predicate Device

The Elecsys CMV IgM Assay is substantially equivalent to other devices legally marketed in the United States and in commercial distribution for the detection of IgM antibodies to cytomegalovirus (CMV) in human serum and plasma.

We claim equivalency to the Diamedix Is-CMV Capture Test Kit (K001767) for the *in vitro* qualitative detection of IgM antibodies to cytomegalovirus (CMV) in human serum and plasma.

The Elecsys PreciControl CMV IgM quality control materials are substantially equivalent to the Roche Elecsys PreciControl Rubella IgM quality control materials cleared in K092322.

1.7.2 Comparison with Predicates: Similarities

Table 1 below provides a comparison of the Elecsys CMV IgM assay and the chosen predicate device, the Diamedix Is-CMV IgM Capture Test Kit (K001767).

Table 1. Comparison of Candidate (Elecsys CMV IgM Assay) and Predicate Device

Feature	Candidate Device Elecsys CMV IgM Assay	Predicate Device Diamedix Is-CMV IgM Capture Test Kit (K001767)
Intended Use/ Indications for Use	Immunoassay for the in vitro qualitative detection of IgM antibodies to CMV in human serum, lithium-heparin plasma, K2-EDTA plasma, and K3-EDTA plasma. The test is intended as an aid in the diagnosis of recent or current CMV infection in individuals for which a CMV IgM test was ordered, including pregnant women. Performance characteristics have not been evaluated in immunocompromised or immunosuppressed individuals. This test is not intended for use in neonatal screening or for use at point of care facilities. This assay is not intended for use in screening blood and plasma donors. The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys immunoassay analyzers.	The Diamedix Is-CMV IgM Capture Test Kit is a capture enzyme immunoassay (EIA) for the qualitative detection of IgM antibodies to CMV in human serum as an aid in the diagnosis of recent or current infection with CMV. These reagents can be used either manually or in conjunction with the MAGO Plus Automated EIA Processor. This product has not been cleared/approved by the FDA for blood/plasma donor screening.
Assay Protocol	µ-Capture	Solid-phase microtiter
Detection Protocol	Electrochemiluminescent Immunoassay	Enzyme-linked immuno-adsorbent assay

1.8 Analytical Performance Data

1.8.1 Precision

The following precision results were obtained with the Elecsys CMV IgM assay in human serum samples and quality control materials. Within-run precision (repeatability) and total imprecision (intermediate precision) were determined according to CLSI Guideline EP5-A2. All results met the pre-defined acceptance criteria for repeatability and intermediate precision.

Table 2. Summary of Precision Results for Elecsys CMV IgM

		Repeatability		Intermediate Precision	
Sample	**Mean (COI)**	**SD**	**CV (%) (UCL95%)**	**SD**	**CV (%) (UCL95%)**
Control 01	0.171	0.003	1.8 (2.9)	0.005	2.9 (4.4)
Control 01	0.220	0.002	0.9 (1.7)	0.007	3.2 (4.6)
Control 02	1.98	0.040	2.0 (2.4)	0.105	5.3 (6.7)
Control 02	2.03	0.032	1.6 (2.1)	0.085	4.2 (5.6)
HS B	0.175	0.003	1.7 (2.8)	0.004	2.3 (3.9)
HS A	0.200	0.002	1.0 (1.7)	0.004	2.0 (3.7)
HS 07	0.249	0.004	1.6 (2.4)	0.007	2.8 (3.7)
HS 04	0.841	0.010	1.2 (1.6)	0.026	3.1 (4.1)
HS 05	0.913	0.013	1.4 (1.8)	0.027	3.0 (4.0)
HS 01	0.957	0.010	1.0 (1.2)	0.031	3.2 (4.4)
HS 06	1.13	0.018	1.6 (2.1)	0.040	3.5 (4.6)
HS 02	1.21	0.016	1.3 (1.7)	0.042	3.5 (4.8)
HS D	1.22	0.022	1.8 (2.2)	0.038	3.1 (3.7)
HS C	1.62	0.024	1.5 (1.8)	0.055	3.4 (4.3)
HS F	4.16	0.067	1.6 (1.9)	0.141	3.4 (4.3)
HS 03	5.07	0.066	1.3 (1.6)	0.157	3.1 (4.1)
HS E	13.9	0.236	1.7 (2.1)	0.445	3.2 (3.9)

1.8.2 Reagent, Sample, Calibration, Calibrator, and Control Stability

Reagent Stability:
Four studies were conducted to evaluate the stability of the Elecsys CMV IgM assay reagent: reagent stability (unopened) at 2 – 8°C, reagent stability (opened) at 2 – 8°C, on-board reagent stability, and reagent stability stored alternately on-board the analyzer and refrigerated.

1. Reagent Stability (Unopened) at 2 – 8°C: Shelf-life reagent stability for the Elecsys CMV IgM assay was tested on one Elecsys 2010 immunoassay analyzer. Three lots of reagent were evaluated using PreciControl CMV IgM (Levels 1 and 2). A fresh kit was placed on the analyzer and calibrated. Reference values for the PreciControl CMV IgM Levels 1 and 2 were then determined. After measurement, the kit was closed and stored refrigerated (2-8°C). The on-test reagent was stored at 2-8°C and PC CMV IgM materials tested in duplicate at several time points and the acceptance criteria were met at each time point. The Elecsys CMV IgM reagent was stable unopened at 2 – 8°C up to 18 months, which supports the claimed shelf life of 15 months.

2. Reagent Stability (Opened) at 2 – 8°C: Reagent stability after first opening for the Elecsys CMV IgM assay was tested on an Elecsys 2010 immunoassay analyzer with duplicate measurements. A fresh kit was placed on the analyzer and calibrated. Reference values for samples on-test were then determined. After measurement, the kit was removed from the analyzer and kept at 2-8°C for up to 13 weeks (92 days). Calibration was repeated and all samples were placed on the analyzer and re-measured. The acceptance criteria were met for reagent stability after opening at 2 – 8°C for 13 weeks, supporting the claim of 12 weeks.

3. On-Board Reagent Stability: On-board reagent stability for the Elecsys CMV IgM assay was tested on one Elecsys 2010 immunoassay analyzer. A fresh kit was placed on the analyzer and calibrated. Reference values for the samples tested were then determined. After measurement, the kits were closed and stored at 20°C ± 3°C to simulate on-board conditions. At specific time points, the kits were placed on the analyzer, calibrated, and the original test samples re-measured. Samples were measured in duplicate with one reagent lot in one run per day. Acceptance criteria were met at each time point for 34 days, supporting the on-board reagent stability claim of 2 weeks.

4. On-Board/Refrigerated Reagent Stability: On-board/refrigerated reagent stability for the Elecsys CMV IgM assay was tested on one Elecsys 2010 immunoassay analyzer by comparing the stressed samples with the reference samples. A fresh kit was placed on the analyzer and calibrated. Reference values for the samples tested were then determined. After measurement, the kit was closed and kept 5x4 hours on-board (20°C ± 3°C) per week; the rest of the time it was stored refrigerated (2-8°C). The acceptance criteria were met, supporting reagent stability up to 6 weeks when stored alternately in the refrigerator and on the analyzer.

Sample Stability:

Four studies were conducted to evaluate sample stability: sample stability at 2 – 8°C, sample stability at 20 – 25°C, sample stability at -20°C, and sample stability through multiple freeze/thaw cycles.

1. Sample Stability at 2 – 8°C: Reference and on-test materials were tested in triplicate on the Elecsys 2010 analyzer. Samples were measured directly after collection (reference) and then stored at 2-8°C for 35 days. These samples were tested after storage at 2-8°C at multiple time points up to 35 days. The on-test recovery was calculated as a percent of the reference value. The acceptance criteria were met, supporting sample stability up to 4 weeks when stored at 2 – 8°C.

2. Sample Stability at 20 – 25°C: Reference and on-test material (human serum and plasma samples) was tested in triplicate and the controls were tested in duplicate on the Elecsys 2010 analyzer. The samples were measured directly after collection (reference) and then stored at 20-25°C for up to 10 days. The on-test recovery was calculated as a percent of or difference from the reference value. The acceptance criteria were met, supporting claimed sample stability up to 7 days at 20 – 25°C,

3. Sample Stability at -20°C: Reference and on-test material was tested in triplicate on the Elecsys 2010 analyzer. The samples were measured immediately after collection (reference) and then stored frozen at -20°C for approximately 4 months (119 days). The samples were re-measured after 119 days of frozen storage at -20°C. The on-test recovery was calculated as a percent of or difference from the reference value. The acceptance criteria were met, supporting claimed sample stability for 3 months at -20°C.

4. Sample Stability Through Multiple Freeze/Thaw Cycles: Reference and on-test material was tested in triplicate on the Elecsys 2010 analyzer. The samples were measured immediately after collection (reference) and aliquots were frozen/thawed 6 times. A sample measurement was taken after each freeze/thaw cycle and the results compared to the reference result. The acceptance criteria were met, supporting claimed sample stability through 5 freeze/thaw cycles,

Calibration Stability:
Two studies were conducted to evaluate calibration stability: lot calibration stability and on-board calibration stability.

1. Lot Calibration Stability: The lot calibration stability was determined by comparing the calibration for two kits of the same lot. On Day 1, the first reagent kit was opened and calibrated, and samples were measured at Days 1 (reference), 29 and 36 on one Elecsys 2010 analyzer. All samples were measured in duplicate with one reagent in one run per day on Days 1, 29, and 36. The acceptance criteria were met for lot calibration stability of 28 days on the Elecsys 2010 analyzer.

2. On-Board Calibration Stability: On-board calibration stability for the Elecsys CMV IgM test system was tested on one Elecsys 2010 analyzer. One reagent kit was

opened and samples were measured on Day 1 (reference). The same samples were then retested after 15 days with reagent bottles stored at 20 ± 3°C (on-board condition) using the calibration from Day 1. Recovery was calculated based on the initial (reference) values. All samples were tested in duplicate with one reagent lot on one Elecsys 2010 analyzer in one run per day on two days. The acceptance criteria were met for on-board calibration stability of 8 days on the Elecsys 2010 analyzer.

Calibrator Stability:
Two studies were conducted to evaluate calibrator stability: calibrator stability at 2 – 8°C and open vial calibrator stability.

1. Calibrator Stability at 2 – 8°C: Reference and on-test materials were tested in duplicate with one reagent lot in one run per day on one Elecsys 2010 analyzer. The on-test material was opened and stored at 2 – 8°C for 8 weeks. It was measured at Day 1 (reference) and again at 8 and 10 weeks. The on-test recovery was calculated as the signal (counts) of the reference value. The acceptance criteria were met for calibrator stability at 2 – 8°C for 8 weeks.

2. Open Vial Calibrator Stability: Reference and open vial, on-test materials were tested in duplicate with one reagent lot on one Elecsys 2010 analyzer. The on-test material was opened and stored at 25°C for 6 hours to simulate on-board conditions. Open vial (on-test) material was also stored at 32°C for 6 hours on one Elecsys 2010 to simulate on-board conditions. Every hour, each calibrator was tested and the on-test recovery of signal (counts) was calculated as a percent of the reference value. The acceptance criteria were met for open vial calibrator stability for 5 hours on the Elecsys 2010 analyzer.

Preci-Control Value Assignment:
The Elecsys CMV IgM calibrators and Elecsys PreciControl CMV IgM values are assigned through at least six independent series of analysis performed on at least three analyzers. All samples are tested in duplicate. The sample recovery (COI) is calculated as the median of each sample as reference to the target value.

Stability of PreciControl CMV IgM:
Three studies were conducted to evaluate the stability of the Elecsys PreciControl CMV IgM materials: control stability at 2 – 8°C, open vial control stability, and shelf-life stability.

1. Control Stability at 2 – 8°C: Stressed and unstressed samples of PreciControl CMV IgM were tested in duplicate with one reagent lot in one run per day on one Elecsys 2010 analyzer. All samples met the acceptance criteria, supporting the claimed PreciControl CMV IgM stability for 8 weeks when stored at 2 – 8°C.

2. Control Open Vial Stability: Reference and open vial, on-test controls were tested in singlicate with one reagent lot on one Elecsys 2010 analyzer. The on-test material was opened, kept at 25°C on the Elecsys 2010 to simulate on-board conditions, and tested every hour for 6 hours. The on-test recovery of signal (counts) was calculated as a percent of the reference value. The acceptance criteria were met, supporting the claimed PreciControl CMV IgM open vial stability of 5 hours on the Elecsys 2010 analyzer.

3. Control Shelf-Life Stability: The on-test material was stored at 2-8°C and tested in duplicate on the Elecsys 2010 analyzer at several time points during and beyond the shelf life time of 18 months. Stability was measured by comparing the measurements of the stressed controls with the measurements of the unstressed controls (reference). The acceptance criteria were met at each time point, supporting the claimed PreciControl CMV IgM shelf-life stability of 15 months.

1.8.3 High Dose Hook Effect
Testing with the Elecsys CMV IgM assay demonstrated no high dose hook effect. Five highly positive, high-titer CMV IgM human samples were diluted with negative human serum in a dilution series with 11 steps. Each dilution was tested in triplicate with one reagent lot in one run on one Elecsys 2010 analyzer. No high dose hook effect was observed up to 32.9 COI.

1.8.4 Cross-Reactivity/Analytical Specificity

A study was conducted to evaluate the Elecsys CMV IgM for potential cross-reactivity using samples from individuals with antibodies to various medical conditions. Specimens (n = 205) were tested in duplicate with the Elecsys CMV IgM assay and a comparator CMV IgM assay. The first result was used for the performance evaluation. The presence of the potential cross-reactants in the samples tested was confirmed using FDA-cleared devices or laboratory methods. Potential cross-reactivity with autoimmune markers and antibodies against influenza vaccination could not be ruled out from the study.

Table 3. Cross-Reactivity Test Results

Potential Cross-Reacting antibodies and disease conditions	Comparator CMV IgM Results (Negative)			Comparator CMV IgM Results (Positive)		
	Elecsys CMV IgM Non-Reactive	Elecsys CMV IgM Indeterminate (Border)	Elecsys CMV IgM Reactive	Elecsys CMV IgM Non-Reactive	Elecsys CMV IgM Indeterminate (Border)	Elecsys CMV IgM Reactive
Autoimmune	5	0	2	0	0	0
EBV	14	0	0	0	0	0
E. coli	5	0	0	0	0	0
HCV	27	0	0	0	0	0
HSV	4	0	0	1	0	0
HTLV	43	0	0	0	0	0
Rubella	10	0	0	0	0	0
HAV	10	0	0	0	0	0
HBV	18	0	0	1	0	0
HIV	20	0	0	1	0	0
Influenza Vaccine	9	0	1	0	0	0
Treponema palladium	4	0	0	0	0	0
Toxoplasma gondii	9	0	0	0	0	0

1.8.5 Endogenous and Drug Interferences

To evaluate the effect of elevated levels of hemoglobin, bilirubin, Intralipid, and biotin on the CMV IgM assay, eight CMV IgM samples (negative, near cutoff and positive) were spiked with the potential interferents. Each interferent was evaluated at 11 numerical values. All samples were tested in singlicate on the Elecsys 2010 analyzer. Acceptance criteria for hemoglobin, bilirubin, Intralipid, and biotin: samples with COI < 0.7 to be found non-reactive, and samples with COI ≥ 0.7 recovery of ±15%.

To evaluate the effect of rheumatoid factor, 34 samples were spiked with different concentrations of RF and measured in singlicate on the Elecsys 2010 analyzer as well as

a comparator device. The acceptance criterion for rheumatoid factor was agreement > 90% against the comparator device.

The results of the interference studies are presented below:

Interferent tested	**No interference up to (Concentration)**
Hemoglobin	< 0.621 mmol/L or < 1.0 g/dL
Bilirubin	< 342 µmol/L or < 20 mg/dL
Intralipid	< 1500 mg/dL
Biotin	< 410 nmol/L or < 100 ng/mL
Rheumatoid factor	< 2000 IU/mL

In addition, 20 pharmaceutical compounds were evaluated for interference with the Elecsys CMV IgM assay. All results met the pre-defined acceptance criteria, demonstrating no interference from the drug substances tested.

Studies were conducted to evaluate the suitability of the following types of samples to be used with the Elecsys CMV IgM immunoassay: Li-heparin plasma, K_2-EDTA plasma, K_3-EDTA plasma, and serum separator tubes. Samples were collected into matched serum and plasma collection tubes and assayed in duplicate. These studies were conducted using negative (non-reactive), near cutoff (indeterminate/border) and positive (reactive) samples. The results support the use of the following sample types: Li-heparin plasma, K_2-EDTA plasma, K_3-EDTA plasma, and serum separator tubes. Acceptance specifications are tabulated below.

Sample Matrix	**Mean COI**	**Percent of samples showing differences in recovery relative to serum (COI) in non-reactive specimens**		
		< 0.07 COI	**0.07 – 0.1 COI**	**> 0.1 COI**
Li-Heparin Plasma	0.196	93 %	7 %	0 %
K_2-EDTA Plasma	0.280	100 %	0 %	0 %
K_3-EDTA Plasma	0.195	97 %	3 %	0 %
Serum Separator Tubes	0.265	100 %	0 %	0 %

Sample Matrix	**Mean COI**	**Percent of samples showing differences in recovery relative to serum (COI) in reactive specimens**		
		< 10 %	**10 – 20 %**	**> 20 %**
Li-Heparin Plasma	1.51	68 %	32 %	0 %
K_2-EDTA Plasma	2.12	100 %	0 %	0 %
K_3-EDTA Plasma	1.72	79 %	21 %	0 %
Serum Separator Tubes	2.27	90 %	10 %	0 %

1.8.6 Method Comparison Between Analyzer Platforms

The equivalence of the Elecsys CMV IgM assay on the Elecsys 2010 and MODULAR ANALYTICS E170 immunoassay analyzers was evaluated by a method comparison study. Native serum samples were tested on one Elecsys 2010 and one MODULAR ANALYTICS E170 analyzer. Positive and negative agreement of the results between the two platforms was calculated and demonstrated equivalence between the analyzer platforms for the determination of IgM antibodies to CMV using the Elecsys CMV IgM assay:

Concordance Rates:
Negative Percent Agreement (NPA) = 97.98 %
Positive Percent Agreement (PPA) = 99.22 %

1.8.7 Assay Cut-Off

The cut-off for the Elecsys CMV IgM assay was established with in-house studies by characterizing samples using several commercially available CMV IgG and CMV IgM assays. Specificity of the assay was evaluated using 931 samples from a low prevalence cohort. The assay cutoff was optimized to increase sensitivity by measuring 152 samples from individuals at different stages of primary CMV infection. Validation of the assay cutoff was performed by external clinical studies.

1.8.8 Verification of IgM Specificity

To confirm that the Elecsys CMV IgM assay specifically detects IgM-class antibodies, 11 samples with moderate to high levels of CMV IgM antibodies were selected for testing. These samples were treated with dithiothreitol (DTT) to destroy the IgM and then were retested using the Elecsys CMV IgM assay. Ten samples were rendered non-reactive (negative) following treatment with DTT, and one sample had an 82% decrease in COI value, confirming the specificity of the Elecsys CMV IgM assay for detecting IgM-class antibodies. The Elecsys CMV IgM assay is specific for anti-CMV IgM antibodies due to the µ-capture design and antigens minimizing interference from CMV IgG antibodies.

1.9 Clinical Performance Data

1.9.1 Reproducibility

The reproducibility was assessed by testing the Elecsys CMV IgM assay on the Elecsys 2010 analyzer at three sites. Imprecision testing was conducted using three replicates in two runs per day for five days consistent with requirements within CLSI EP5-A2 and EP15-A2 with four serum pools and two PreciControl CMV IgM materials. One reagent lot was used for all of the testing at all three sites. The sample panels evaluated included samples close to the cutoff, reactive and non-reactive. All sample panels demonstrated a CV % less than 10 % and the results are presented in the table below.

Table 4. Elecsys CMV IgM Clinical Reproducibility

			Repeatability		**Between-Day**		**Between-Site**		**Reproducibility**	
Sample	**n**	**Mean COI[a]**	**SD[b]**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**
HSP 01 Near Cut-Off	90	0.839	0.012	1.4	0.000[c]	0.0	0.039	4.6	0.043	5.1
HSP 02 Near Cut-Off	90	1.094	0.016	1.5	0.000[c]	0.0	0.047	4.3	0.052	4.8
HSP 03 Reactive	90	5.156	0.126	2.4	0.027	0.5	0.058	1.1	0.186	3.6
HSP 04 Non-Reactive	90	0.242	0.003	1.3	0.002	0.7	0.023	9.6	0.024	9.8
PC CMV-IgM_1 Negative	90	0.207	0.003	1.6	0.003	1.4	0.019	9.2	0.020	9.5
PC CMV-IgM_2 Positive	90	1.851	0.042	2.3	0.000[c]	0.0	0.042	2.3	0.079	4.2

[a] COI - Cutoff index
[b] SD - Standard deviation
[c] SD of zero due to variance contributed by particular component was below stated significant figure.

1.9.2 Method Comparison

A multi-center study was conducted in the US to evaluate the performance of the Elecsys CMV IgM immunoassay in comparison to a consensus result derived from 2 or 3 FDA-cleared devices (depending on the availability of sample volume for testing). A two-out-of-three approach was used to determine the consensus result for samples where three FDA-cleared devices could be tested. Where only two FDA-cleared devices could be tested, results for which the FDA-cleared devices disagreed were omitted from analysis. All equivocal results obtained using the Elecsys CMV IgM assay were treated as not in favor of the Elecsys CMV IgM assay.

The main study was a prospective study consisting of 617 samples, all of which were from a population of patients suspected of CMV infection for whom a CMV IgM test was ordered. A subset of this population (n = 199) were pregnant women. In addition, a retrospective study was conducted, consisting of 134 samples that were preselected from a population of patients positive for CMV IgM as determined by the comparator device consensus of 3 FDA-cleared CMV IgM assays. Testing of specimens was done at three clinical sites and one internal site. The results of these studies are presented in the following tables.

Table 5. Prospectively Collected Suspected Infection Population

		Comparator Device Consensus CMV IgM Result			
		Positive	**Equivocal**	**Negative**	**Total**
Elecsys CMV IgM Result	**Reactive**	20	0	6	26
	Indeterminate (Border)	0	0	5	5
	Non-Reactive	0	3[a]	384	387
	Total	20	3	395	418

Agreement Classification	**Numerator/ Denominator**	**Percent Agreement (%)**	**95% Confidence Interval**
Negative Agreement	384/395	97.2	95.1 – 98.6
Positive Agreement	20/23	87.0	66.4 – 97.2

[a] These samples were Equivocal according to the consensus result and Non-reactive (negative) by the Elecsys CMV IgM assay. As such, they were treated as Elecsys CMV IgM Reactive (positive) in the analysis (i.e., not in favor of the Elecsys CMV IgM assay).

Table 6. Prospectively Collected Pregnant Population

		Comparator Device Consensus CMV IgM Result			
		Positive	**Equivocal**	**Negative**	**Total**
Elecsys CMV IgM Result	**Reactive**	0	0	2	2
	Indeterminate (Border)	1	0	1	2
	Non-Reactive	0	5	190	195
	Total	1	5	193	199

Agreement Classification	**Numerator/ Denominator**	**Percent Agreement (%)**	**95% Confidence Interval**
Negative Agreement	190/193	98.5	95.5 – 99.7
Positive Agreement	0/6	0.00	0.00 – 45.9

Table 7. Preselected Confirmed CMV IgM Positive Population

		Comparator Device Consensus CMV IgM Result			
		Positive	**Equivocal**	**Negative**	**Total**
Elecsys CMV IgM Result	**Reactive**	134	0	0	134
	Indeterminate (Border)	0	0	0	0
	Non-Reactive	0	0	0	0
	Total	134	0	0	134

Agreement Classification	**Numerator/ Denominator**	**Percent Agreement (%)**	**95% Confidence Interval**
Negative Agreement	N/A[b]		
Positive Agreement	134/134	100.0	97.3 – 100.0

[b] The number of negative samples in this study was not sufficient (and not required) to make statistically valid conclusions about the negative percent agreement.

1.9.3 Expected Values/Reference Range

The observed expected values in the prospectively collected US clinical study population using the Elecsys CMV IgM assay were as follows:

Table 8. Expected Values—Elecsys CMV IgM Assay

		Elecsys CMV IgM Result			
Age Group (years)	**Sex**	**Reactive N (%)**	**Indeterminate (Border) N (%)**	**Non-Reactive N (%)**	**Total (N)**
18 – 19	Female	0 (0.00)	0 (0.00)	2 (100.00)	2
	Male	0 (0.00)	0 (0.00)	5 (100.00)	5
20 – 29	Female	2 (1.96)	1 (0.98)	99 (97.06)	102
	Male	0 (0.00)	2 (4.44)	43 (95.56)	45
30 – 39	Female	2 (1.23)	2 (1.23)	159 (97.55)	163
	Male	1 (1.30)	2 (2.60)	74 (96.10)	77
40 – 49	Female	1 (3.03)	0 (0.00)	32 (96.97)	33
	Male	0 (0.00)	0 (0.00)	70 (100.00)	70
50 – 59	Female	2 (12.50)	0 (0.00)	14 (87.50)	16
	Male	1 (1.67)	0 (0.00)	59 (98.33)	60
60 – 69	Female	0 (0.00)	0 (0.00)	6 (100.00)	6
	Male	1 (5.56)	0 (0.00)	17 (94.44)	18
70 – 79	Male	0 (0.00)	0 (0.00)	2 (100.00)	2
Totals	Female	7 (2.17)	3 (0.93)	312 (96.89)	322
	Male	3 (1.08)	4 (1.44)	270 (97.47)	277
	Overall	10 (1.67)	7 (1.17)	582 (97.16)	599